

## REMARKS

The Office Action has maintained the restriction requirement and has only examined the claims of elected Group I, i.e., Claims 57-64 and 66-71. Claims 57-64 and 66-71 are rejected under 35 U.S.C. §101 for an alleged lack of patentable utility. In addition, Claims 57-64 and 66-71 are rejected under 35 U.S.C. §112, for allegedly being non-enabling. Finally, Claim 66 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants are submitting the following Remarks, which are deemed to place the present case in condition for allowance.

Pursuant to the rejection of Claims 57-64 and 66-71 under 35 U.S.C. §101, the Office Action alleges that the claimed subject matter is not useful. According to the Office Action, the application relates to pharmaceutical compositions comprising a compound of Formula I and a compound having vitamin PP activity, selected from the group of compounds of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb. The Office Action states that the specification indicates that the compounds of Formula I are used as cancerostatic agents and/or tumor inhibitors or immunosuppressive agents, while the compounds having vitamin PP activity are alleged to have cytoprotective activity for the “prevention, reduction or elimination of side effects and/or neutralization of the effects of cancerostatic agents or immunosuppressive agents”. (Emphasis in Original). The Office Action alleges that the claimed composition encompasses “millions of possible compounds and combination of compounds” and that it is not apparent which combination of compounds will have the biological effects alleged in the specification.” The Office Action characterizes the utility as a “mere scientific curiosity”. Moreover, the Office Action also alleges that utility is lacking, alleging that the compounds having vitamin PP activity neutralizes the effects of the

compounds of Formula I. The Office Action further alleges that the specification only provides for tests of compound of Formula I with two different agents having vitamin PP activity. According to the Office Action, nicotinanide not only decreases the cytotoxicity of K.22.097, but also appears to inhibit its efficacy. Thus, according to the Office Action, it is not apparent that the claimed compositions have utility in treating a human patient.

Applicants strongly disagree. The present application meets the requisite utility under 35 U.S.C. §101.

To satisfy the utility requirement of 35 U.S.C. §101, the claimed invention must be useful, i.e., it must have a specific and substantial utility. Fujikawa v. Wattanasin, 93 F3d 1559, 1563, 39 USPQ2d 1895, 1898-1899 (Fed. Cir. 1996). In other words, one skilled in the art can use a claimed discovery in the manner which provides some immediate benefit to the public. Nelson v. Bowler, 626 F2d 853, 856, 206 USPQ 881, 883 (CCPA 1980). It is well settled that where an applicant has established utility for a species that falls within an identified genus of compounds, and presents a generic claim covering the genus, as a general matter, that claim should be treated as being sufficient under 35 U.S.C. §101. MPEP §2107.02. Moreover, an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not credible do not render the claimed invention lacking in utility. See, e.g., Raytheon v. Roper, 724 F2d, 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984).

Here the application has a substantial utility. The present invention is directed, inter alia, to a pharmaceutical composition comprising at least one cancerostatic or immunosuppressive agent of Formula I and at least one compound having vitamin PP activity or an ester thereof. Thus,

part of the utility comes from the compounds of Formula I, the utility being a cancerostatic or immunosuppressive agent.

Applicants have shown by the data on pages 110 *et seq.* of the application using an exemplary compound of Formula I, that those compound have anti-tumor activity. In addition, applicants have provided in US Patent 6,506,572 data of additional compounds falling within the scope of formula I, herein showing anti-tumor activity, e.g. see the data in table 5 respecting such compounds as K22130, K22132, K22133, K221316, K22339, and K22365. Moreover applicants have elucidated therein the mechanism by which the compounds of Formula I act on the human organism. See U.S. Patent No. 6,506,572, Column 7, Line50 and Column 8, Line 55. As described therein, applicants have determined that the compounds, especially inhibit the cellular formation of niacinamide mononucleotide; by employing these compounds of Formula I, many malignant cells are affected.

Part of the utility comes from the compounds having PP activity. With respect to the compounds having PP activity, the application states that these compounds (1) prevent, reduce or eliminate side effects of cancerostatic agents or immunosuppressive agents, especially compounds of formula I and/or (2) neutralize the effects of the cancerostatic and immunosuppressive use agents. Thus, there are two utilities attributed to the effect of the compounds having PP activity. One of the utilities is to reduce the side effects of the compounds of Formula I. Applicants have demonstrated using exemplary compounds that these compounds effectively reduce the side effects. As described hereinabove, applicants have shown the cancerostatic effect of the compounds of Formula I, for example, K22097. See the data in Tables 1, 2, 3, 4, 5 on pages 111-114 of the instant specification. Moreover, attention is directed to Table 4 on page 114, which shows that a representative compound having vitamin PP activity reduces and/or eliminates the adverse effects of the compounds of Formula

I. More specifically, when K22097 was given to a test animal, i.e., mice, at concentration at  $2 \times 100$  mg/kg, 1 mice died, while at a dosage of  $2 \times 120$  mg/kg, 3 mice died. On the other hand, when an exemplary compound having PP activity, e.g., nicotinamide, was administered simultaneously with the anti-tumor agent, no mice had died, thereby showing that the combination prevented a side effect of the anti-tumor agent, namely death. Moreover, the data in Table 4 also show that the administration of K22097 to the mice reduced leukocyte cells, while the co-administration of K22097 and nicotinamide prevented the reduction of leukocyte cells.

Thus, applicants have shown that the combination has a substantial and specific utility. More specifically, they have shown that the drugs of Formula I have anti-tumor activity and that the side effects, which are associated with cancerostatic therapy, can be reduced, eliminated or prevented using the compounds having vitamin PP activity.

Moreover, the data also show that it may be helpful to suppress the cancerostatic activity of the compounds of Formula I to raise the surviving rate of the non-tumor cells.

Thus, the specification provides sufficient teaching to show that the combination has a useful utility, and accordingly have met the utility requirement.

Further, applicants have shown that one embodiment, K22.097 and nicotinamide, a species within the genus of Claim 1, exhibits anti-tumor activity with reduced side effects. Accordingly, the generic claim covering the genus is to be treated as having sufficient utility under 35 U.S.C. §101. See MPEP 2107.02.

Accordingly, this rejection is overcome; withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 57-64 and 66-75 under 35 U.S.C. §112, first paragraph, the Office Action alleges that the application lacks enablement. Applicants respectfully

disagree. The claimed subject matter is enabled. To show this, applicants have considered the Wands factors as recited in the Office Action.

1. The nature of the invention, state of the prior art, and the predictability of the art.

The nature of the invention is directed to a pharmaceutical composition comprising a compound of formula I and a compound having vitamin PP activity of or on having the compounds of Formula II, IIa, IIb, IIIa, IIIb, IIIc, IV, IVa, IVb, Va and Vb exhibiting anti-tumor and immunosuppressive activity with reduced side effects.

The Office Action avers that the nature of this art is unpredictable citing articles by Sausville et al. and Johnson et al. The two documents contradict traditionally explored tumor model systems and their transfer to the treatment of human or animal patients. Furthermore, Johnson et al. teach that in-vivo activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. But, both these references raise the issue of applicability of the predictive value with respect to models using engrafts of human tumors grown in immuno deficient mice. The present application does not utilize these models; thus the conclusions in the cited references are irrelevant.

Moreover, applicants have shown using representative compounds that the composition of the present invention does have the requisite utility. For example, attention is directed to Example 1-5 which shows that a representative compound of Formula I, e.g., K22097 has anti-tumor activity. Furthermore, as described herein above, attention is directed to US Patent No. 6,506,752 which provides data of additional compounds of Formula I evidencing the anti-tumor effect therof. See Table 5 therein.

Moreover, attention is directed to pages 110-115 of the specification which provides detailed experimental support for the neutralization of the growth-inhibiting effect of anti tumor

agents by nicotinic acid and niacinamide, both compounds of which are representative members of the vitamin PP group, demonstrated by using human leukemia cells (Example 1), normal lymphocytes (Example 2), intestine cells (Example 3) and NMRI mice (Example 4). In addition, for example, pages 6-28 teaches the general classes of compounds and pages 28-33 teaches representative and specific compounds having vitamin PP activity.

Furthermore, the test protocols described on pages 110 to 115 of the specification are but some of the well-established methods for determining the ability of compounds, such as the vitamin PP compounds of the invention, to suppress the side effects of anti tumor agents. Therefore, the utility does not rely on heretofore generally unknown or undescribed research methods or techniques, but clearly shows the efficacy of the composition of the present invention.

In its rejection, the Office Action alleges that the applicants do not provide a mechanism of action. But, there is no requirement in patent law that the applicant must understand how the invention works to obtain a patent.

In addition, applicants successfully elucidated the mechanism by which the compounds of Formula I act on the human organism. See U.S. Patent No. 6,506,572, which describes in this patent, compounds which fall within the scope of Formula I. As described in Column 7, Line 50 to Column 8 Line 55, therein, these compounds inhibit the cellular formation of niacinamide mononucleotide.

Moreover, the compounds having vitamin PP activity reduce the side effects of the drugs of Formula I. Therefore, the prevention, reduction or elimination of the side effects of the compounds of Formula I are achieved through the administration of a compound having vitamin PP activity to the patient as disclosed in the present patent application.

2. The amount of direction or guidance provided at the presence or absence of working examples.

The Office Action questions whether compounds of Formula I have the requisite utility. Applicants have provided working examples. See examples 1-5 which demonstrates the anti-tumor activity of the compounds of Formula I. This data is supplemented by the data in US Patent No 6,506,572 which discloses in Table 2 several compounds which fall within the scope of Formula I, such as K22.130, K22.132, K22.133, K22.316, K22.339, and K22.365. As shown by the data in Table 5, these compounds have anti-tumor activity. The data in Tables 1-4 teach the co-administration of the anti-tumor substance K22.097 and nicotinamide or nicotinic acid as representative of vitamin PP compounds in laboratory models using cells from a human monocytic leukemia, normal lymphocytes, cryptic cells of the large intestine and in NMRI mice. Again, attention is directed to the data in Table 4 on page 114, which show that the cases of death caused by the anti-tumor substance as well as the strong reduction of leucocyte cells could be completely prevented by the co-administration of a compound of Formula I and a compound having Vitamin PP activity .

It is evident from the experimental results in Tables 1-5 that the use of the compounds of vitamin PP group is capable of suppressing the unavoidable side effects of anti-tumor agents.

Further, the application teaches how to administer the compounds of Formula I and the compounds having anti-vitamin PP activity. Attention is directed to page 62, line 11 to page 79, line 19, which indicates the therapeutic formulations and the preparation thereof and the dosage amounts of the compounds, so that one of ordinary skill in the art can administer these compounds as cancerostatic or tumor inhibiting or immunosuppressive agents with reduced side effects to subjects without an undue amount of experimentation.

3. The quantity of experimentation necessary.

Thus, based on the above, there is sufficient evidence in the record that shows that the compounds of Formula I have anti-tumor activity. Moreover, the disclosure contains a teaching of the manner and process for preventing, reducing, eliminating or neutralizing the side effects of cancerostatic or immunosuppressive agents of Formula I by administering a compound having vitamin PP activity.

Further, the detailed working Examples 1-4 on pages 110-115, which demonstrates that “the cases of death caused by the anti-tumor substances as well as the strong reduction of leucocyte cells could be completely prevented” by the administration of compounds having vitamin PP activity and that “the use of compounds of the vitamin PP group according to the invention is capable of suppressing the unavoidable side-effects of anti-tumor substances.” See page 115 of the specification.

Furthermore, as the CCPA states in In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971), “A specification disclosure that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.” And “it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumably accurate disclosure.”

The Office Action failed to provide any evidence whatsoever, which disputes the utility alleged by applicants. It did not provide any articles or treaties or any other evidence, which refuses the utility of the composition of the present invention. It did not provide any reasoning or rationale which is inconsistent with the statements that the present composition has the requisite utility. It just concludes that due to the lack of evidence, the applicants have not shown the utility. However, the burden is on the USPTO to show that the present composition does not have the requisite utility. The USPTO did not meet that burden.

Thus, for the reasons given, applicants respectfully submit that the specification provides all information needed for the person of ordinary skill in the art to practice the claims without undue experimentation and that Claims 57-64 and 66-71 are enabled by the specification. Withdrawal of the rejection is requested.

Pursuant to the rejection of Claim 66 under 35 U.S.C § 112, first paragraph, the Office Action alleges that the application does not have descriptive support for the esters of a compound having vitamin PP activity.

Applicants respectfully disagree. Case law has held that the first paragraph of 35 U.S.C. §112, requires that the specification shall contain a written description of the invention. Vas-Cath Inc. v. Mahurkea, 935 F2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). The written description requirement has several policy objectives, but the essential goal of the description requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. In re Barker, 559 Fd 588, 592 n. 4, 194 USPQ 470, 473 n.4 (CCPA 1977). The written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based and to demonstrate that the

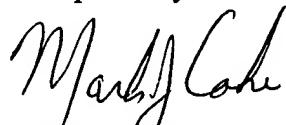
patentee was in possession of the invention that is claimed. Capon v. Eshhar, 418F3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). An adequate written description of the invention may be shown by any description of sufficient, relevant identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. Vas-Cath Inc. v. Makurkar, 935 F2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

There is no question that the underlying specification provides support for the compounds of Formula II, IIa, IIb, IIIa, IIIb, IIIc, IV, IVA, IVB, V, Va and Vb, a position with which the USPTO concurs. However, as described on page 55, line 13 of the instant specification, the inventors also contemplated esters thereof. One of ordinary skill in the art understands the definition of an ester, being a derivative of a carboxylic acid. It is also clear that the substituents R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, include hydroxy, carboxy or hydroxyalkyl, that is, groups which can be esterified. Since the base structure of the above compounds are the same, one of ordinary skill in the art understands what is meant by converting those groups to esters. These esters are a specific carboxylic acid derivatives having an acyl group. Esters are specific groups, they are not e.g. alcohols, amines, ketones, aldehydes, etc. They are identifiable having identifying characteristics. Thus, by using the term "esters", as recited in the specification and claims, it is clear to one of ordinary skill in art that the inventors had possession of esters of the compounds having Vitamin PP activity recited above at the time of the filing of the application. Thus, applicants respectfully submit that there is adequate written support for "esters," in accordance with the description requirement under 35 U.S.C. §112, first paragraph. Therefore, this rejection is obviated; withdrawal thereof is respectfully requested.

Thus, in view of the Remarks herein, it is respectfully submitted that the present case

is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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